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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/980,403 | 04/15/2002 | Donald Gullberg | 000510-010 | 3147 |

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| EXAMINER | |
|---|---|
| HADDAD, MAHER M | |
| **ART UNIT** | **PAPER NUMBER** |
| 1644 | |

DATE MAILED: 05/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/980,403 | GULLBERG, DONALD | |
| | Examiner | Art Unit | |
| | Maher M. Haddad | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *21 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 13, 22 and 150-152* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/21/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-10,12,13,15-19,21,22,26,27,29-93,95-105,107-112,114,117,118,120,125,127-145,147,148 and 150-152.
Continuation of Disposition of Claims: Claims withdrawn from consideration are 2-10,12,15-19,21,26,27,29-93,95-105,107-112,114,117,118,120,125,127-145,147 and 148.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 3/21/05, is acknowledged.

2. Claims 1-10, 12-13, 15-19, 21-22, 26-27, 29-93, 95-105, 107-112, 114, 117-118, 120, 125, 127-145, 147-148 and 150-152 are pending.

3. Claims 2-10, 12, 15-19, 21, 26, 27, 29-93, 95-105, 107-112, 114, 117, 118, 120, 125, 127-145, 147-148 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 1, 13, 22 and 150-152 are under consideration in the instant application as they read on a recombinant or isolated integrin subunit α11 having the amino acid sequence encoded by SEQ ID NO: 1, fragments thereof and a composition thereof.

5. Applicant's IDS, filed 3/21/05, is acknowledged.

6. In view of the amendment filed on 3/21/05, only the following rejections are remained.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

*The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.*

8. Claims 1, 13, 22 and 150-152 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling an isolated integrin subunit α11 having the amino acid sequence of SEQ ID NO: 2 or fragments thereof, wherein the fragments are selected from the group consisting og a peptide consisting of the amino acid sequence from the cytoplasmic domain from amino acid 1165-1188 of SEQ ID NO:2, the amino acid sequence of the extracellular domain from amino acid 804-826 of SEQ ID NO:2, the amino acid of the I-domain from amino acid 159-355 of SEQ ID NO: 2, a composition thereof; a heterodimer comprising α11β1; a composition thereof a fragment consisting of the amino acid sequence KLGFFRSARRRREPGLDPTPKVLE, the extracellular domain consisting of amino acids 804-826 of SEQ ID NO:2, the I-domain consisting of amino acid 159 to 355 of SEQ ID NO:2 and a composition thereof, does not reasonably provide **enablement** for a recombinant or isolated integrin subunit α11 "having" "fragments" of SEQ ID NO: 2, wherein the fragments are selected from the group consisting of a peptide "comprising" the amino acid sequence from the cytoplasmic domain from amino acid 1165-1188, 804-826 and 159-355 of SEQ ID NO: 2 in claim 1 and 22 or a recombinant or isolated integrin heterodimer comprising a "fragment and a subunit β1" in claim 13 or a "pharmaceutical" composition comprising as the components of

claims 1, 13, or 22, in claims 150-152. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim for the same reasons set forth in the previous Office Action mailed 10/21/04.

Claim 13 recites a heterodimer of a fragment of SEQ ID NO: 2 and a β1 subunit. However, a specific binding site of the α subunit is required to form a heterodimer with β subunits. The specification fails to teach which fragment of SEQ ID NO: 2 binds to β1 subunit and forms a heterodimer. It is unclear whether the claimed fragments would form a heterodimer with the β1 subunit since the interaction between the α and β subunits requires the I-domain of the α subunit to fold before association with the β subunit. Further, the I-domain has about 200 amino acids of the alpha subunit.

The terms "comprising" and "having" in claims 1 and 22 is open ended and extend the fragment peptides to include additional on either or both sides of the cytoplasmic domain of SEQ ID NO: 3, I-domain (aa 159-355) and the extracellular domain (aa 804-826), other than the pepeptide consisting of SEQ ID NO: 3, aa804-826 or aa159-355. It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions can result in substantially different biological activities. Because of the lack of sufficient guidance and predictability in determining which modifications would lead to the collagen type I binding and that the relationship between the peptide and its activity was not well understood. It would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of fragments of integrin subunit α11 that binds collagen type I. Without sufficient guidance, the changes which can be made in the structure of "fragment" and still provide collagen type I binding activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Further, at issue is whether or not the claimed composition would function as a pharmaceutical composition. In view of the absence of a specific and detailed description in Applicant's specification of how to effectively use the composition as claimed, and absence of working examples providing evidence which is reasonably predictive that the claimed compositions are effective for in vivo use, and the lack of predictability in the art at the time the invention was made, an undue amount of experimentation would be required to practice the claimed pharmaceutical composition with a reasonable expectation of success. If the use disclosed is of such nature that the art is unaware of successful treatments with chemically analogous compounds, a more complete statement of how to use must be supplied.

Applicant's arguments, filed 3/21/05, have been fully considered, but have not been found persuasive.

Applicant submits that the skilled person could make such a fragment comprising such peptides and test it for desired properties without undue experimentation. Applicant points to the specification for support on how to test a peptide fragment for collagen-binding activity by

chromatographic means. Further, Applicant submits that testing a given fragment of the integrin subunit sequence of SEQ ID NO: 2 to determine whether it retains the desired properties could readily be accomplished without undue experimentation.

However, while experimental testing techniques using cell surface receptor binding compounds are available, it is not routine in the art to use such methods when the expectation of success is unpredictable based on the instant disclosure. Thus, it would require an undue amount of experimentation of one skilled in the art to practice the invention as broadly claimed.

Regarding the pharmaceutical composition, Applicant submits that the Examiner has acknowledged in paragraph 13 of the Office Action that the specification is enabling for pharmaceutical composition.

Applicant appears to mischaracterize the rejection of record with respect to the pharmaceutical composition. While the Examiner states that the specification is enabled for a composition comprising the claimed polypeptide, however, the examiner clearly states that the lack of in vivo efficacy for the claimed polypeptide renders the vaccine and hence the pharmaceutical composition not enabled.

9. Claims 1, 13, 22 and 150-152 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons set forth in the previous Office Action mailed 10/21/04.

Applicant is in possession an isolated integrin subunit α11 having the amino acid sequence of SEQ ID NO: 2 or fragments thereof, wherein the fragments are selected from the group consisting og a peptide consisting of the amino acid sequence from the cytoplasmic domain from amino acid 1165-1188 of SEQ ID NO:2, the amino acid sequence of the extracellular domain from amino acid 804-826 of SEQ ID NO:2, the amino acid of the I-domain from amino acid 159-355 of SEQ ID NO: 2, a composition thereof; a heterodimer comprising α11β1; a composition thereof a fragment consisting of the amino acid sequence KLGFFRSARRRREPGLDPTPKVLE, the extracellular domain consisting of amino acids 804-826 of SEQ ID NO:2, the I-domain consisting of amino acid 159 to 355 of SEQ ID NO:2 and a composition thereof.

Applicant is not in possession of a recombinant or isolated integrin subunit α11 "having" "fragments" of SEQ ID NO: 2, wherein the fragments are selected from the group consisting of a peptide "comprising" the amino acid sequence from the cytoplasmic domain from amino acid 1165-1188, 804-826 and 159-355 of SEQ ID NO: 2 in claim 1 and 22 or a recombinant or isolated integrin heterodimer comprising a "fragment and a subunit β1" in claim 13 or a "pharmaceutical" composition comprising as the components of claims 1, 13, or 22, in claims 150-152.

Applicant's arguments, filed 3/21/05, have been fully considered, but have not been found persuasive.

Applicant incorporates the comments discussed in the enablement rejection to the written description rejection.

The Examiner's rebuttal is same as in the enablement rejection above.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

*(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.*

10. Claims 1, 13, and 151-152 are rejected under 35 U.S.C. 102(b) as being anticipated by Gullberg *et al* (Dev. Dyn. 204:57-65, 1995) (IDS Ref. No. C2), as is evidenced by Velling *et al* (IDS Ref. No. C5) for the same reasons set forth in the previous Office Action mailed 10/21/04.

Claims 151 and 152 are included because the claimed composition reads on a compound without a carrier. Further, Gullberg *et al* teach the αmt in a TBS buffer (see page 64 under immunoprecipitation and electrophoresis) which is considered an acceptable carrier.

Applicant's arguments, filed 3/21/05, have been fully considered, but have not been found persuasive.

Applicant submits that Gullberg et al did not extend to cloning or sequencing of the cDNA encoding amount. Further, Gullberg et al contains no amino acid or nucleotide sequence information. In addition there is no indication from Gullberg et al that amount is the same as the α11 integrin subunit of the present invention. Applicant further contends that no research group has ever verified the sequence of the integrin subunit in Gullberg et al to be same as that of the α11 integrin subunit. Applicant strongly disagree with the examiner conclusion that the amino acids of αmt, α11 and SEQ ID NO: 2 are the same base on Velling evidentiary reference. Applicant argues that Velling et al conclusions are based solely on the "similar behavior" exhibited by α11 integrin and αmt. Applicant submits that there is no evidence in Velling et al to suggest that the sequence of α11 integrin subunit of the present invention is the same as αmt. Applicant further submits that Velling et al merely speculates that the proteins are the same but has no evidence to support this speculation. Applicant submits that it is well established in the law that an anticipatory reference must be enabling and it is equally well recognized in the law that mere speculation is insufficient without more to provide adequate enablement. Applicant further, argues that Gullberg et al states that the amt subunit also demonstrates behavioral

similarities with integrin subunits other than α11. Applicant characterizes Velling et al conclusion that αmt is identical to α11 as inconclusive and ambiguous evidence. Applicant further submits that two proteins with a similar function can have different amino acid sequences. Applicant argues that α11 integrin and αmt, whilst appearing to share functional properties, actually have different sequences. Applicant submits that α11 integrin was isolated from a uterus cDNA library while αmt was identified in fetal muscle cells. Applicant submits that the two integrin chains were identified in different tissue types. Furthermore the tissue-specific isoforms of proteins can exist and that these isoforms may have a similar function but differ in terms of amino acid sequence. Applicant concludes that such tissue-specific isoforms of the protein would be highly likely to have different amino acid sequences. Applicant submits that the subject of the amended claims is not rendered obvious by the teachings of Gullberg et al. It is evident from Gullberg et al that cloning the gene encoding the integrin αmt subunit was problematic. Applicant submits that a skilled person would not have a reasonable expection of success of isolating the integrin αmt subunit. Applicant submits that he was not able to isolate the α11 subunit using the methods disclosed in Gullberg et al. Applicant further, argues that microsequencing of the resulting proteins revealed the presence of α2 integrin, however, the α11 protein seemed to dissociate and passed through the column in the flow-through. Applicant concludes that the α11 was not sequenced and could not be purified by this method.

However, Applicant's own specification on page 25, line 32-37 and postdated publication (Velling et al) discloses that "[B]based on similar SDS-PAGE migration patterns, similar behavior under reducing conditions, association with b1 integrin chain, and upregulation during in vitro differentiation of human fetal myoblasts, the present data show that α11 integrin is identical with αmt." Gullberg et al (1995) teach the isolation of αmt having a molecular weight of 145 kDa which is distinctly larger than 140 kD α2 integrin chain when analyzed by SDS-PAGE under non-reducing conditions. The specification discloses that the claimed α11 integrin chain is 145 kD under non-reducing condition (see page 4, line 26 in particular). A comparison of the instant products with prior art indicates that αmt is "identical" with α11. Therefore, SEQ ID NO: 2 is inherent property of αmt taught by Gullberg et al. Sequencing αmt integrin subunit is only further characterization of the isolated αmt taught by Gullberg et al. Regarding the argument that αmt subunit isolation was problematic, the examiner notes that the patentablility of a product does not depend on its method of production. In re Thorpe, 227 USPQ 964,966 (fed.Cir. 1985) see MPEP 2113. Regarding the argument that Gullberg et al reference does contain no amino acid or nucleotide sequence information. Cloning and sequencing of a known product is only further characterization of the know product. In response to applicant argument that Velling teachings are mere speculation, the examiner notes that applicant own specification also admits that the αmt is identical with α11. Thus, faced with the disclosure that αmt is identical with α11 results, the examiner's position is that αmt subunit anticipates α11 subunit in the absence of showing to the contrary.

11. No claim is allowed.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maher Haddad, Ph.D.
Patent Examiner
May 9, 2005

Christina Chan

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